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STANTON, R — EXAMINER

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This is a communication from the examiner in charge of your application.
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For Restriction Purposes Only

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 0 month(s), 30 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-62 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☐ Claims _____ are rejected.
5. ☐ Claims _____ are objected to.
6. ☑ Claims 1-62 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Claims 1-62 are pending in the instant Application.

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-5 and 33-38, drawn to methods for treating cytokine mediated toxicity comprising inhibiting MIF biologic activity, classified in various classes and subclasses dependent upon the nature of the inhibitor; for example, methods employing antibodies are classified in Class 424, subclass 130.1.

Claims 1-5 are generic to a plurality of disclosed patentably distinct species comprising:

a. using anti-MIF antibodies (claim 3);
b. using soluble MIF receptors (claim 4);
c. using small organic molecules (claim 5)

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. Following said election, the claims of the instant invention will only be examined to the extent that they read on the elected species. Claims not directed to said species will be **WITHDRAWN** from consideration.

The species delineated above are distinct, one from the other because they utilize materially different biologic agents each of which requires separate areas of search and consideration. For example, species (a) requires search and consideration of antibodies; species (b) of altered forms of cellular receptors; and species (c) of undefined non-protein, agents.

II. Claims 6-10 and 33-38, drawn to methods for treating cytokine mediated toxicity comprising inhibiting MIF receptor biologic activity, classified in various classes and subclasses dependent upon the nature of the inhibitor; for example, methods employing antibodies are classified in Class 424, subclass 130.1.

Claims 6-10 are generic to a plurality of disclosed patentably distinct species comprising:

a. using anti-MIF-receptor antibodies (claim 8);
b. using inactive MIF analogs (claim 9);
c. using small organic molecules (claim 10)

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. Following said election, the claims of the instant invention will only be examined to the extent that they read on the elected species. Claims not directed to said species will be **WITHDRAWN** from consideration.

The species delineated above are distinct, one from the other because they utilize materially different biologic agents each of which requires separate areas of search and consideration. For example, species (a) requires search and consideration of antibodies; species (b) of altered forms of cellular receptors; and species (c) of undefined non-protein, agents.

III. Claims 11-15 and 33-38, drawn to methods for treating cytokine mediated toxicity comprising inhibiting MIF gene expression, classified in various classes and subclasses dependent upon the nature of the inhibitor; for example, methods employing antisense nucleic acids are classified in Class 514, subclass 44.

Claims 11-15 are generic to a plurality of disclosed patentably distinct species comprising:

a. using antisense nucleic acids (claim 12);
b. using ribozymes (claim 13);
c. using triple helix components (claim 14);
d. using steroids (claim 15).

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. Following said election, the claims of the instant invention will only be examined to the extent that they read on the elected species. Claims not directed to said species will be **WITHDRAWN** from consideration.

The species delineated above are distinct, one from the other because they utilize materially different biologic agents each of which requires separate areas of search and consideration. Species (a)-(c) utilize distinct nucleic acids with distinct properties. For example, search and consideration of antisense nucleic acids requires analysis of nucleic acids that bind to other nucleic acids and inhibit transcription or translation; analysis of ribozymes requires analysis of nucleic acids that cleave other nucleic acids; and analysis of triplex nucleic acids requires search and consideration of nucleic acids capable of forming alternative nucleic acid structures. Species (d) is distinct from species (a)-(c) because species (d) does not utilize nucleic acids and requires search of the steroid art.

IV. Claims 16-19 and 33-38, drawn to methods for treating cytokine mediated toxicity comprising inhibiting MIF-receptor gene expression, classified in various classes and subclasses dependent upon the nature of the inhibitor; for example, methods employing antisense nucleic acids are classified in Class 514, subclass 44.

Claims 16-19 are generic to a plurality of disclosed patentably distinct species comprising:

a. using antisense nucleic acids (claim 17);
b. using ribozymes (claim 18);

c. using triple helix components (claim 19).

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. Following said election, the claims of the instant invention will only be examined to the extent that they read on the elected species. Claims not directed to said species will be **WITHDRAWN** from consideration.

The species delineated above are distinct, one from the other because they utilize materially different biologic agents each of which requires separate areas of search and consideration. Species (a)-(c) utilize distant nucleic acids with distinct properties. For example, search and consideration of antisense nucleic acids requires analysis of nucleic acids that bind to other nucleic acids and inhibit transcription or translation; analysis of ribozymes requires analysis of nucleic acids that cleave other nucleic acids; and analysis of triplex nucleic acids requires search and consideration of nucleic acids capable of forming alternative nucleic acid structures.

V. Claims 20-26 and 33-38, drawn to methods for treating cytokine mediated toxicity comprising inhibiting MIF release, classified in various classes and subclasses dependent upon the nature of the inhibitor.

VI. Claims 27-38, drawn to combination therapies for treatment of cytokine mediated toxicity, classified in various Classes and subclasses dependent upon the agent used.

Claims 27-32 are generic to a plurality of disclosed patentably distinct species and subspecies comprising:

A. Agent (a):

a. using agents that inhibit MIF biologic activity;

1. using MIF antagonists (claim 28);

i. using anti-MIF antibodies (claim 29);
ii. using soluble MIF receptors (claim 30);
iii. using soluble TNFα receptor (claim 31);
iv. using soluble IL-1 receptor (claim 31);
v. using soluble IFN-γ (claims 31);
vi. using small organic molecules (claim 32)

b. using agents that inhibit MIF receptor biologic activity;
c. using agents that inhibit MIF gene expression;
d. using agents that inhibit MIF receptor gene expression;
e. using agents that inhibit MIF release;

B. Agent (b):

a. using anti-TNFα;
b. using anti-IL-1;
c. using anti-IFN-γ;
d. using IL-1RA;
e. using a steroid;
f. using a glucocorticoid;
g. using IL-10;

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. Following said election, the claims of the instant invention will only be examined to the extent that they read on the elected species. Claims not directed to said species will be **WITHDRAWN** from consideration.

In regard to species (A)(a)-(A)(e) above, each particular mechanism of inhibiting MIF biologic activity is distinct from the other because they proceed via materially different processes that require separate areas of search and consideration. For example, the species (A)(a) and (A)(b) requires search and consideration of the biological activity of distinct proteins (MIF or MIF receptor); species (A)(c) and (A)(d) require search and consideration of the alteration of gene expression of separate genes (those encoding MIF or MIF receptor, respectively); and species (A)(e) requires search and consideration of cellular and molecular control of MIF release.

In regard to the different species (B)(a)-(B)(g), each requires search and consideration of materially different agents that have separate and distinct effects and targets within an animal. For example, species (B)(a)-(B)(c) utilize antibodies that bind to separate proteins, each protein having distinct biochemical and biological properties. Therefore, each species (B)(a)-(B)(c) requires separate search of each antibody target. Species (B)(d)-(B)(g) utilize distinct, non-antibody agents that would have been expected to have had separate effects within in host. Therefore, analysis of each of these species requires a search in the non-patent literature that is specific for each agent.

Note that claims 33-38 are multiply dependent and depend from several distinct inventions. Therefore, upon election of a single invention and a single species, claims 33-38 **will only be examined to the extent that they read on said invention and species.**

VII. Claims 39 and 40, drawn to methods of inhibiting the toxic side effects of steroids, classified in various Classes and subclasses dependent upon the agent used.

VIII. Claims 41 and 42, drawn to methods of enhancing anti-inflammatory activity of steroids, classified in various Classes and subclasses dependent upon the agent used.

IX. Claims 43 and 44, drawn to methods of assaying for MIF, classified in Class 435, subclass 7.2.

X. Claims 45-53, drawn to methods of identifying compounds that inhibit MIF release, classified in Class 435, subclass 4.

XI. Claims 54 and 55, drawn to MIF receptor proteins, classified in Class 530, subclass 350.

XII. Claim 56, drawn to recombinant cell lines, classified in Class 435, subclass 240.1.

XIII. Claims 57-60, drawn to transgenic animals expressing modified MIF, classified in Class 800, subclass 2.

XIV. Claims 61 and 62, drawn to anti-MIF antibodies, classified in Class 530, subclass 387.1.

Should applicant traverse any species election on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

The inventions are distinct, each from the other because of the following reasons:

The inventions of groups I, III and V are each distinct from either of the inventions of groups II and IV, because the latter inventions are targeted to modulation of the MIF activity, expression, or release while the latter inventions are directed to modulation of MIF receptor activity or expression. Therefore, analysis of the inventions require distinct areas of search in the non-patent literature, said search directed towards the molecules being modulated.

The inventions of groups I, III and V are distinct, one from the other, because they involve distinct methods of modulating MIF activity and each method requires separate areas of search and consideration. For example, the methods of group I require search of MIF biological activity and methods of modulating said activity; the methods of group III require search of means of altering gene expression; and the methods of group V require search of the mechanism of MIF release. Similarly, the inventions of groups II and IV are distinct, one from the other, because they utilize materially different methods of modulating MIF receptor activity. For example, the invention of group II requires consideration of MIF receptor activity and therefore a search directed towards the biochemistry of said receptor is required. In contrast, the methods of group IV are directed to modulation of MIF receptor

gene activity and the corresponding analysis requires search of the MIF receptor gene and means of modulating gene expression.

The methods of any of groups I-V are distinct from the methods of group VI, because the latter methods utilize combination therapies using multiple therapeutic agents. Therefore, search of the methods of group VI must encompass multiple therapeutic agents as well as the interaction between said agents.

Any of the methods of groups I-VI are distinct from any of the methods of groups VII-X, because the former groups of inventions are drawn to methods of treating cytokine mediated toxicity and none of the latter methods are so directed. Therefore, a search of cytokine mediated toxicity, *per se*, is not required for analysis of any of the latter methods.

The methods of groups VII-VIII are distinct, one from the other, because they are drawn to materially different processes each requiring separate areas of search and consideration. For example, the methods of group VII are directed towards modulation of side effects of steroid treatment which requires search directed toward such side-effects. The methods of group VIII are directed towards enhancing steroid activity *in vivo* and analysis of such methods requires search of steroid activity *per se*. Thus, the searches required for the two sets of methods are non-coextensive.

Either of the methods of groups VII or VIII are distinct from either of the methods of groups IX or X because the former methods are directed towards modulation of *in vivo* effects, whereas the latter take place *in vitro*. Therefore, analysis of the latter methods do not require search or consideration of means of modulating *in vivo* biologic effects.

The methods of groups IX and X are distant, one from the other, because they are drawn to materially different methods. For example, the methods of group IX are directed towards identification of MIF by a direct binding assay whereas the latter methods utilize tissue culture cells to measure biological activity. Thus, the search of the former methods need not include cell culture or biological activity assays *per se*.

The methods of group I-IX are distinct from any of the compounds of groups XI-XIII, because the latter compounds are not utilized in any of said methods and therefore search of said compounds *per se* are not required for analysis of any of said methods. Similarly, the invention of group X is distinct from any of the inventions of groups XI-XIV because the compounds and compositions of the latter groups of inventions are not used in the invention of group X and therefore examination of the invention of group X does not require search or consideration of said compounds or compositions.

Any of the inventions of groups I, II, VI, and IX and the invention of group XIV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following

can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the antibodies of the invention of group XIV may be used in materially different methods as evidence by their use in the methods of groups I, II, and VI.

Any of the methods of groups III-V, VII, VIII, and X are distinct from the antibodies of groups XIV, because said antibodies are not used in said methods and therefore search of said antibodies *per se* is not required for analysis of said methods.

The compounds and compositions of the inventions of groups XI-XIV are distinct, one from the other because they are drawn to materially different substances each of which requires a separate area of search and consideration. For example, the invention of group XI is drawn to MIF proteins; the invention of group XII is drawn to cell lines; the invention of group XIII is drawn to transgenic animals; and the invention of group XIV is drawn to antibodies. Therefore, the separate inventions require divergent areas of search tailored to the specification compounds and compositions claimed.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classifications, recognized divergent subject matter and further because the searches required for the different inventions are not coextensive, restriction for examination purposes as indicated is proper.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian R. Stanton whose telephone number is (703) 308-2801. The examiner can normally be reached Monday-Thursday from 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax phone number for this Group is (703) 308-4312.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Brian R. Stanton, Ph.D.
07 September 1995

BRIAN R. STANTON
PATENT EXAMINER
GROUP 1800